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(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
9 November 2000 (09.11.2000)

PCT

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**WO 00/66753 A3**

- (51) International Patent Classification<sup>7</sup>: C12N 15/57, 15/12, 9/64, C07K 14/745, A61K 38/36, 38/48, C12N 5/10, C12Q 1/37
- (74) Agent: ELLINGER, Mark, S.; Fish & Richardson P.C., P.A., 60 South Sixth Street, Suite 3300, Minneapolis, MN 55402 (US).
- (21) International Application Number: PCT/US00/11416
- (22) International Filing Date: 28 April 2000 (28.04.2000)
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- (30) Priority Data:  
09/302,239 29 April 1999 (29.04.1999) US
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:  
US 09/302,239 (CON)  
Filed on 29 April 1999 (29.04.1999)
- (71) Applicant (for all designated States except US): REGENTS OF THE UNIVERSITY OF MINNESOTA [US/US]; 600 University Gateway, 200 Oak Street S.E., Minneapolis, MN 55455-2020 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): NELSESTUEN, Gary, L. [US/US]; 1514 Fulham Street, St. Paul, MN 55455 (US).
- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— With international search report.
- (88) Date of publication of the international search report:  
26 April 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MODIFIED VITAMIN K-DEPENDENT POLYPEPTIDES

(57) Abstract: The invention provides vitamin K-dependent polypeptides with enhanced membrane binding affinity. These polypeptides can be used to modulate clot formation in mammals. Methods of modulating clot formation in mammals are also described.

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*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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EE	Estonia						

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 09531/016WO1		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/11416	International filing date (day/month/year) 28/04/2000	Priority date (day/month/year) 29/04/1999	
International Patent Classification (IPC) or national classification and IPC C12N15/57			
Applicant REGENTS OF THE UNIVERSITY OF MINNESOTA et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the report</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV <input checked="" type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI <input checked="" type="checkbox"/> Certain documents cited</li> <li>VII <input type="checkbox"/> Certain defects in the international application</li> <li>VIII <input type="checkbox"/> Certain observations on the international application</li> </ul>			
Date of submission of the demand 29/11/2000		Date of completion of this report 24.07.2001	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer  Vollbach, S  Telephone No. +49 89 2399 8715	



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/11416

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-56 as originally filed

**Claims, No.:**

1-75 as originally filed

**Drawings, sheets:**

1/16-16/16 as originally filed

**Sequence listing part of the description, pages:**

3-7 (sheet 1/5-5/5), filed with the letter of 27.7.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/11416

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 7-15, 44-47 completely, 1-6,31,39-43,51-58,75 partially.

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
  - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
  - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
  - ☒ no international search report has been established for the said claims Nos. 7-15,44-47 completely, 1-6,31,39-43,51-58,75 partially.
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
  - ☐ the computer readable form has not been furnished or does not comply with the standard.

**IV. Lack of unity of invention**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/11416

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	11,36,14,31,39-42
	No:	Claims	1-10,13,15,43-47,51-58,75
Inventive step (IS)	Yes:	Claims	
	No:	Claims	11,36,14,31,39-42
Industrial applicability (IA)	Yes:	Claims	1-6,31,39-43,51-58,75
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/11416

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**2. Non-written disclosures (Rule 70.9)**

**see separate sheet**

1. The Search authority found multiple inventions covered by the present application. Due to the failure to pay additional fees, search has only been carried out partially i.e. claims 7-15 completely, claims 1-6,31,39-43,51-58 and 75 partially. As a consequence, examination can also be based only on said subject-matter.

2. The above mentioned claims relate to vitamin K-dependent polypeptides which have been modified by substitutions in the GLA domains resulting in inhibition of clot formation.

In particular, the protein is protein C or activated protein C. Substitutions have been carried out at various positions, e.g amino acid residue 5,9,11,12,29,33,34,35 or 36. The present application further relates to modified protein C which in addition include an inactivated cleavage site, and those which have an insertion at position 4 resulting in a modified protein C which exhibits enhanced membrane binding activity. Within the scope of the claims nucleic acid molecules encoding these proteins, pharmaceutical compositions and methods are embraced.

3. The following documents are referred to in the present report:

D1: The Journal of biological Chemistry, vol. 273, no. 47, 1998, Shen et al.

D2: Biochemistry, vol.36, No. 17,1997, McDonald et al.

Both documents describe modified protein C for improving membrane binding activity and/ or influencing clot formation. In particular, the sites under investigation common to those claimed in the present application are amino acid residue 4,5,9,11,12,33 and 34. The medical benefit of these modified proteins is also disclosed.

In view of said documents present claims 1-10,13,15,43-47,51-58 and 75 are no longer new as required by Article 33(2) PCT.

As a consequence of said novelty objection, lack of unity a posteriori arises. A common inventive concept linking together the different protein C substitutions does no longer exist. This applies especially with regard to claim 31 and claims 39-41 but also for any single protein C substitution mentioned in claim 2.

In the present phase the applicant will not be invited to pay additional fees. However, said objection will be prosecuted once the application enters the regional phase.

For those modifications of protein C which are not disclosed in the prior art documents,



an inventive step cannot be recognized. This is reasoned by the fact that any tool and method for identifying further mutants which exhibit e.g improved membrane binding or activity is at the disposal of a skilled person and can thus be applied in analogous manner as already applied successfully in the prior art. Therefore present claims 11,36,14,31 and 39-42 are inadmissible under Article 33(3) PCT.

4. For the assessment of the present claims 53 and 54 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5. Certain cited documents  
WO 99/20767

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
US Department of Commerce  
United States Patent and Trademark  
Office, PCT  
2011 South Clark Place Room  
CP2/5C24  
Arlington, VA 22202  
ETATS-UNIS D'AMERIQUE  
in its capacity as elected Office

Date of mailing (day/month/year) 16 January 2001 (16.01.01)	
International application No. PCT/US00/11416	Applicant's or agent's file reference 09531/016WO1
International filing date (day/month/year) 28 April 2000 (28.04.00)	Priority date (day/month/year) 29 April 1999 (29.04.99)
Applicant NELSESTUEN, Gary, L.	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
29 November 2000 (29.11.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer R. E. Stoffel Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREA

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>09531/016W01</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 00/ 11416</b>	International filing date (day/month/year) <b>28/04/2000</b>	(Earliest) Priority Date (day/month/year) <b>29/04/1999</b>
Applicant <b>REGENTS OF THE UNIVERSITY OF MINNESOTA et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.  
☐ It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).
3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:

Docketed By Practice Systems

Search Report - Response

Due: 3/15/01

Initials: *meaney*5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.



None of the figures.

Form PCT/ISA/210 (first sheet) (July 1998)

Docketed By Billing Secretary

Due Date: 3/15/01

Deadline: 3/15/01

Initials: *AS*

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/11416

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 C12N15/57 C12N15/12 C12N9/64 C07K14/745 A61K38/36 A61K38/48 C12N5/10 C12Q1/37		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12N C07K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BIOSIS, WPI Data		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 20767 A (UNIV MINNESOTA) 29 April 1999 (1999-04-29)  the whole document	1-15, 43-47, 51-58,75
X	& ZA 9 809 597 A (UNIV MINNESOTA) 23 April 1999 (1999-04-23) ---	
X	SHEN L ET AL: "Enhancing the activity of protein C by mutagenesis to improve the membrane-binding site: studies related to proline-10" BIOCHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. EASTON, PA, vol. 36, no. 51, 23 December 1997 (1997-12-23), pages 16025-16031, XP002092844 ISSN: 0006-2960	1,2,4,7, 44, 51-58,75
Y	the whole document ---	2,3
-/--		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search  <div style="text-align: center; font-size: 1.2em;">11 October 2000</div>		Date of mailing of the international search report  <div style="text-align: center; font-size: 1.2em;">15. 01. 01</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  <div style="text-align: center; font-weight: bold;">VAN DER SCHAAL C.A.</div>

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/11416

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHEN LEI ET AL: "Enhancement of human protein C function by site-directed mutagenesis of the gamma-carboxyglutamic acid domain." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 47, 20 November 1998 (1998-11-20), pages 31086-31091, XP002149742 ISSN: 0021-9258	1,2,4, 7-10,13, 43,44, 46, 51-58,75
Y	the whole document	2,3
Y	--- MCDONALD J F ET AL: "Comparison of naturally occurring vitamin K - dependent proteins: correlation of amino acid sequences and membrane binding properties suggests a membrane contact site" BIOCHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. EASTON, PA, vol. 36, no. 17, 29 April 1997 (1997-04-29), pages 5120-5127, XP002092840 ISSN: 0006-2960 the whole document -----	2,3

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/11416

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9920767 A	29-04-1999	US 6017882 A	25-01-2000
		AU 2702499 A	10-05-1999
		BR 9814611 A	03-10-2000
		NO 20002025 A	19-06-2000
		ZA 9809597 A	23-04-1999
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# INTERNATIONAL SEARCH REPORT

national application No.  
PCT/US 00/11416

## Box I Observations where certain claims were found uns archable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 53 and 54 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: -  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
  
Claims 7-15 completely, 1-6, 31, 39-43, 51-58, 75 partially.

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 7-15 44-47 completely,  
1-6 31 39-43 51-58 75 partially

Protein C with modified GLA domain, its use and nucleic acids encoding it

2. Claims: 16-20 32 33 48 49 60-62 64 65 67 68 completely  
1-6 31 39-43 51-59 63 66 70-75 partially

Factor VII with modified GLA domain, its use and nucleic acids encoding it

3. Claims: 21-26 completely 1-6 31 39 40 43 50-58 75  
partially

Protein S with modified GLA domain, its use and nucleic acids encoding it

4. Claims: 27-30 69 completely 1-6 31 39 43 50-59 63 66  
70-75 partially

Factor IX with modified GLA domain, its use and nucleic acids encoding it

5. Claims: 34-36 1-6 31 39 40 43 51-53 55-58 75 partially

Factor X with modified GLA domain, its use and nucleic acids encoding it

6. Claims: 37 38 completely 1-6 31 39 43 51-53 55-58 75  
partially

Protein Z with modified GLA domain, its use and nucleic acids encoding it



From the:  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ELLINGER, Mark S.  
FISH & RICHARDSON, P.C., P.A.  
60 South Sixth Street  
Suite 3300  
MINNEAPOLIS, MINNESOTA 55402  
ETATS-UNIS D'AMERIQUE

PCT

WRITTEN OPINION

(PCT Rule 66)

MAR 14 2001

PRACTICE SYSTEMS

Date of mailing  
(day/month/year) 02.03.2001

Applicant's or agent's file reference  
09531/016WO1

**REPLY DUE** within 3 month(s)  
from the above date of mailing

International application No.  
PCT/US00/11416

International filing date (day/month/year)  
28/04/2000

Priority date (day/month/year)  
29/04/1999

International Patent Classification (IPC) or both national classification and IPC

C12N15/57

Applicant

REGENTS OF THE UNIVERSITY OF MINNESOTA et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain document cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Docketed By Billing Secretary

Due Date: 6/2/01

Deadline: 6/2/01

Initials: DAS CAT

3. The applicant is hereby invited to reply to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

**Also:** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 29/08/2001.

Docketed By Practice Systems

Response to Written Opinion

Base: 3/2/01

Due: 6/2/01

Initials: Jmeany

Name and mailing address of the international preliminary examining authority:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Vollbach, S

Formalities officer (incl. extension of time limits)

Guerin, A

Telephone No. +49 89 2399 8061



**I. Basis of the opinion**

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

**Description, pages:**

1-56 as originally filed

**Claims, No.:**

1-75 as originally filed

**Drawings, sheets:**

1/16-16/16 as originally filed

**Sequence listing part of the description, pages:**

3-7 (sheet 1/5-5/5), filed with the letter of 27.7.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

### III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 7-15, 44-47 completely, 1-6,31,39-43,51-58,75 partially,

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
  - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
  - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
  - ☒ no international search report has been established for the said claims Nos. 7-15,44-47 completely, 1-6,31,39-43,51-58,75 partially.
2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
  - ☐ the computer readable form has not been furnished or does not comply with the standard.

### IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:  
**see separate sheet**
3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:
- ☒ all parts.
- ☐ the parts relating to claims Nos. .

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement
- |                               |        |                           |
|-------------------------------|--------|---------------------------|
| Novelty (N)                   | Claims | 1-10,13,15,43-47,51-58,75 |
| Inventive step (IS)           | Claims | 11,36,14,31,39-42         |
| Industrial applicability (IA) | Claims |                           |
2. Citations and explanations  
**see separate sheet**

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)  
and / or
2. Non-written disclosures (Rule 70.9)  
**see separate sheet**

1. The Search authority found multiple inventions covered by the present application. Due to the failure to pay additional fees, search has only been carried out partially i.e. claims 7-15 completely, claims 1-6,31,39-43,51-58 and 75 partially. As a consequence, examination can also be based only on said subject-matter.

2. The above mentioned claims relate to vitamin K-dependent polypeptides which have been modified by substitutions in the GLA domains resulting in inhibition of clot formation.

In particular, the protein is protein C or activated protein C. Substitutions have been carried out at various positions, e.g amino acid residue 5,9,11,12,29,33,34,35 or 36. The present application further relates to modified protein C which in addition include an inactivated cleavage site, and those which have an insertion at position 4 resulting in a modified protein C which exhibits enhanced membrane binding activity. Within the scope of the claims nucleic acid molecules encoding these proteins, pharmaceutical compositions and methods are embraced.

3. The following documents are referred to in the present report:

D1: The Journal of biological Chemistry, vol. 273, no. 47, 1998, Shen et al.

D2: Biochemistry, vol.36, No. 17,1997, McDonald et al.

Both documents describe modified protein C for improving membrane binding activity and/ or influencing clot formation. In particular, the sites under investigation common to those claimed in the present application are amino acid residue 4,5,9,11,12,33 and 34. The medical benefit of these modified proteins is also disclosed.

In view of said documents present claims 1-10,13,15,43-47,51-58 and 75 are no longer new as required by Article 33(2) PCT.

As a consequence of said novelty objection, lack of unity a posteriori arises. A common inventive concept linking together the different protein C substitutions does no longer exist. This applies especially with regard to claim 31 and claims 39-41 but also for any single protein C substitution mentioned in claim 2.

In the present phase the applicant will not be invited to pay additional fees. However, said objection will be prosecuted once the application enters the regional phase.

For those modifications of protein C which are not disclosed in the prior art documents,

an inventive step cannot be recognized. This is reasoned by the fact that any tool and method for identifying further mutants which exhibit e.g improved membrane binding or activity is at the disposal of a skilled person and can thus be applied in analogous manner as already applied successfully in the prior art. Therefore present claims 11,36,14,31 and 39-42 are inadmissible under Article 33(3) PCT.

4. Certain cited documents  
WO 99/20767

5. For the assessment of the present claims 53 and 54 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The demand must be filed with the competent International Preliminary Examining Authority or, if two or more Authorities are with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line  
IPEA/ EP

**PCT**

**CHAPTER II**

**DEMAND**

under Article 31 of the Patent Cooperation Treaty:  
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
<b>Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION</b>		Applicant's or agent's file reference 09531-016WO1	
International application No. PCT/US00/11416	International filing date (day/month/year) 28 April 2000 ( 28.04.00 )	(Earliest) Priority date (day/month/year) 29 April 1999 ( 29.04.99 )	
Title of invention MODIFIED VITAMIN K-DEPENDENT POLYPEPTIDES			
<b>Box No. II APPLICANT(S)</b>			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) REGENTS OF THE UNIVERSITY OF MINNESOTA 600 University Gateway 200 Oak Street S.E. Minneapolis, Minnesota 55455-2020 United States of America		Telephone No.:	
		Facsimile No.:	
		Teleprinter No.:	
State (that is, country) of nationality: US		State (that is, country) of residence: US	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) NELSESTUEN, Gary L. 1514 Fulham Street St. Paul, Minnesota 55455 United States of America			
State (that is, country) of nationality: US		State (that is, country) of residence: US	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)			
State (that is, country) of nationality:		State (that is, country) of residence:	
<input type="checkbox"/> Further applicants are indicated on a continuation sheet.			

**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The following person is ☒ agent ☐ common representative  
 and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.  
☐ is hereby appointed and any earlier appointment of (an) agent(s) /common representative is hereby revoked.  
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official  
The address must include postal code and name of country.)*

ELLINGER, Mark S.  
 Fish & Richardson P.C., P.A.  
 60 South Sixth Street, Suite 3300  
 Minneapolis, Minnesota 55402  
 United States of America

Telephone No.:  
 (612) 335-5070

Facsimile No.:  
 (612) 288-9696

Teleprinter No.:

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:\***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed.

the description ☒ as originally filed  
☐ as amended under Article 34

the claims ☒ as originally filed  
☐ as amended under Article 19 (together with any accompanying statement)  
☐ as amended under Article 34

the drawings ☒ as originally filed  
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

\* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

- ☒ which is the language in which the international application was filed.  
☐ which is the language of a translation furnished for the purposes of international search.  
☐ which is the language of publication of the international application.  
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

**Box No. V ELECTION OF STATES**

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:



**Box No. VI CHECK LIST**

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- |   |   |        |
|---|---|--------|
| 1. translation of international application                             | : | sheets |
| 2. amendments under Article 34  | : | sheets |
| 3. copy (or where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter   | : | sheets |
| 6. other ( <i>specify</i> )   | : | sheets |

For International Preliminary  
Examining Authority use only

- |                          |                          |
|--------------------------|--------------------------|
| received                 | not received             |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |

The demand is also accompanied by the item(s) marked below:

- |  |   |
|--|---|
| 1. <input checked="" type="checkbox"/> fee calculation sheet                             | 4. <input type="checkbox"/> statement explaining lack of signature                                  |
| 2. <input type="checkbox"/> separate signed power of attorney                            | 5. <input type="checkbox"/> nucleotide and or amino acid sequence listing in computer readable form |
| 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: | 6. <input checked="" type="checkbox"/> other ( <i>specify</i> ): Form 1037.1                        |

**Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE**

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

  
Monica McCormick Graham Reg. # 42,600

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference  
(if desired) (12 characters maximum) 09531/016WO1

Box No. I TITLE OF INVENTION  
MODIFIED VITAMIN K-DEPENDENT POLYPEPTIDES

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

REGENTS OF THE UNIVERSITY OF MINNESOTA  
Morrill Hall  
100 Church Street S.E.  
Minneapolis, Minnesota 55455  
United States of America

☐ This person is also-inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State (that is, country) of nationality:  
US

State (that is, country) of residence:  
US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

NELSESTUEN, Gary L.  
1514 Fulham Street  
St. Paul, Minnesota 55455  
United States of America

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
US

State (that is, country) of residence:  
US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent ☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

ELLINGER, Mark S.  
Fish & Richardson P.C., P.A.  
60 South Sixth Street, Suite 3300  
Minneapolis, Minnesota 55402  
United States of America

Telephone No.  
612/335-5070

Facsimile No.  
612/288-9696

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

**Box No.V DESIGNATION OF STATES**

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):


**Regional Patent**

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

**National Patent (if other kind of protection or treatment desired, specify on dotted line):**

- |  |  |
|--|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates                  | <input checked="" type="checkbox"/> LR Liberia                                   |
| <input checked="" type="checkbox"/> AL Albania                               | <input checked="" type="checkbox"/> LS Lesotho                                   |
| <input checked="" type="checkbox"/> AM Armenia                               | <input checked="" type="checkbox"/> LT Lithuania                                 |
| <input checked="" type="checkbox"/> AT Austria                               | <input checked="" type="checkbox"/> LU Luxembourg                                |
| <input checked="" type="checkbox"/> AU Australia                             | <input checked="" type="checkbox"/> LV Latvia                                    |
| <input checked="" type="checkbox"/> AZ Azerbaijan                            | <input checked="" type="checkbox"/> MA Morocco                                   |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina                | <input checked="" type="checkbox"/> MD Republic of Moldova                       |
| <input checked="" type="checkbox"/> BB Barbados                              | <input checked="" type="checkbox"/> MG Madagascar                                |
| <input checked="" type="checkbox"/> BG Bulgaria                              | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BR Brazil                                |  |
| <input checked="" type="checkbox"/> BY Belarus                               | <input checked="" type="checkbox"/> MN Mongolia                                  |
| <input checked="" type="checkbox"/> CA Canada                                | <input checked="" type="checkbox"/> MW Malawi                                    |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein  | <input checked="" type="checkbox"/> MX Mexico                                    |
| <input checked="" type="checkbox"/> CN China                                 | <input checked="" type="checkbox"/> NO Norway                                    |
| <input checked="" type="checkbox"/> CR Costa Rica                            | <input checked="" type="checkbox"/> NZ New Zealand                               |
| <input checked="" type="checkbox"/> CU Cuba                                  | <input checked="" type="checkbox"/> PL Poland                                    |
| <input checked="" type="checkbox"/> CZ Czech Republic                        | <input checked="" type="checkbox"/> PT Portugal                                  |
| <input checked="" type="checkbox"/> DE Germany                               | <input checked="" type="checkbox"/> RO Romania                                   |
| <input checked="" type="checkbox"/> DK Denmark                               | <input checked="" type="checkbox"/> RU Russian Federation                        |
| <input checked="" type="checkbox"/> DM Dominica                              | <input checked="" type="checkbox"/> SD Sudan                                     |
| <input checked="" type="checkbox"/> EE Estonia                               | <input checked="" type="checkbox"/> SE Sweden                                    |
| <input checked="" type="checkbox"/> ES Spain                                 | <input checked="" type="checkbox"/> SG Singapore                                 |
| <input checked="" type="checkbox"/> FI Finland                               | <input checked="" type="checkbox"/> SI Slovenia                                  |
| <input checked="" type="checkbox"/> GB United Kingdom                        | <input checked="" type="checkbox"/> SK Slovakia                                  |
| <input checked="" type="checkbox"/> GD Grenada                               | <input checked="" type="checkbox"/> SL Sierra Leone                              |
| <input checked="" type="checkbox"/> GE Georgia                               | <input checked="" type="checkbox"/> TJ Tajikistan                                |
| <input checked="" type="checkbox"/> GH Ghana                                 | <input checked="" type="checkbox"/> TM Turkmenistan                              |
| <input checked="" type="checkbox"/> GM Gambia                                | <input checked="" type="checkbox"/> TR Turkey                                    |
| <input checked="" type="checkbox"/> HR Croatia                               | <input checked="" type="checkbox"/> TT Trinidad and Tobago                       |
| <input checked="" type="checkbox"/> HU Hungary                               | <input checked="" type="checkbox"/> TZ United Republic of Tanzania               |
| <input checked="" type="checkbox"/> ID Indonesia                             | <input checked="" type="checkbox"/> UA Ukraine                                   |
| <input checked="" type="checkbox"/> IL Israel                                | <input checked="" type="checkbox"/> UG Uganda                                    |
| <input checked="" type="checkbox"/> IN India                                 | <input checked="" type="checkbox"/> US United States of America continuation of  |
| <input checked="" type="checkbox"/> IS Iceland                               | US 09/302,239 filed 29 April 1999  |
| <input checked="" type="checkbox"/> JP Japan                                 | <input checked="" type="checkbox"/> UZ Uzbekistan                                |
| <input checked="" type="checkbox"/> KE Kenya                                 | <input checked="" type="checkbox"/> VN Viet Nam                                  |
| <input checked="" type="checkbox"/> KG Kyrgyzstan                            | <input checked="" type="checkbox"/> YU Yugoslavia                                |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> ZA South Africa                              |
|  | <input checked="" type="checkbox"/> ZW Zimbabwe                                  |
| <input checked="" type="checkbox"/> KR Republic of Korea                     | Check-boxes reserved for designating States which have become                    |
| <input checked="" type="checkbox"/> KZ Kazakhstan                            | party to the PCT after issuance of this sheet:                                   |
| <input checked="" type="checkbox"/> LC Saint Lucia                           | <input checked="" type="checkbox"/> all eligible countries.                      |
| <input checked="" type="checkbox"/> LK Sri Lanka                             |  |

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

<b>Box No. VI PRIORITY CLAIM</b>					<input type="checkbox"/> Further priorities are indicated in the Supplemental Box.				
Filing date of earlier application (day/month/year)		Number of earlier application		earlier application is:					
				national application: country		regional application: regional Office		international application: receiving Office	
item (1) 29 April 1999		09/302,239		US					
item (2)									
item (3)									
<input checked="" type="checkbox"/> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): <u>item (1)</u> <small>* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.</small>									
<b>Box No. VII INTERNATIONAL SEARCHING AUTHORITY</b>									
Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): <b>ISA/EP</b>					Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year)      Number      Country (or regional Office)				
<b>Box No. VIII CHECK LIST: LANGUAGE OF FILING</b>									
This international application contains the following number of sheets: request : 3 description (excluding sequence listing part) : 56 claims : 7 abstract : 1 drawings : 16 sequence listing part of description : _____ Total number of sheets : 83					This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input type="checkbox"/> separate signed power of attorney 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input checked="" type="checkbox"/> other (specify): transmittal letter; postcard; check				
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